REMARKS

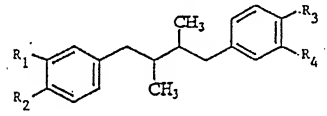
Claims 9-10, 15, 18-20 and 32-37 are pending and under examination. New claims 38-42 have been added. Support for the new claims can be found throughout the specification, e.g. in example 9. No new matter has been added. Reconsideration is requested.

I. Rejections Based on Howell

a. Anticipation

The Examiner has maintained his rejection of claims 9, 10, 15 and 18-20 under 35 U.S.C. §102 as being anticipated by United States patent number 5,541,232 to Howell ("Howell") This rejection is traversed for the following reasons.

Each of claims 9, 10, 15 and 18-20 is directed to the treatment of leukemia through the administration of a "composition consisting essentially of an effective amount of formula

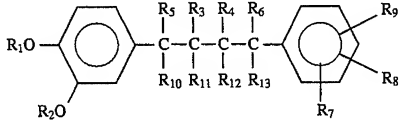


wherein R_1, R_2, R_3, and R_4 independently represent -OH, -OCH_3, -O(C=O)CH_3, or a substituted or unsubstituted amino acid residue or salt thereof, but are not each -OH simultaneously; and optionally one or more pharmaceutically acceptable excipients or carriers; and (b) administering the composition to an individual in need of treatment."

1. Howell does not teach use of NDGA Alone to treat Leukemia

The Examiner takes the position that Howell teaches the administration of NDGA alone to treat leukemia. In support of this position, the office action cites the abstract of Howell and column 5, lines 10-41. These provisions on their face fail to teach the use of NDGA to treat the leukemia itself, but rather are drawn to treating multidrug resistance along with a separate antineoplastic agent.

The Howell abstract on its face states that the NDGA is used to treat multidrug resistance.

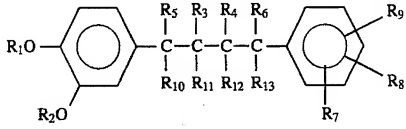
> A method and composition for treating multidrug resistance in a mammal, in which the composition includes NDGA or an analog of NDGA in accordance with the following formula:
>
> 
>
>
> wherein R_1 and R_2 are independently H, lower alkyl or lower acyl; R_3, R_4, R_5, and R_6 are independently H or lower alkyl; R_7, R_8 and R_9 are independently H, hydroxy, lower alkoxy or lower acyloxy; and R_{10}, R_{11}, R_{12} and R_{13} are independently H or lower alkyl, in a pharmaceutically acceptable vehicle. The method is particularly suitable for administering an antineoplastic agent, and the composition includes the combination of NDGA, or an analog with such an antineoplastic agent.
> (emphasis supplied, Abstract)

Similarly, the other provisions cited by the examiner also fail to teach the use of NDGA or its derivatives as antineoplastic agents.

> The present invention provides a method and composition for the inhibition and/or reversal of multidrug resistant phenomenon in a patient and thereby treatment of solid malignant tumors and hematological malignancies comprising the administration of NDGA to said patient preferably in a pharmaceutically acceptable vehicle.

The general formula comprises of from about 0.1% to about 25% NDGA or an analogue thereof in a pharmaceutically acceptable vehicle for topical application or of from about 1 mg NDGA to about 500 mg of NDGA per kg of body weight for systemic administration.

NDGA and its analogues used in the present invention have the following Formula (I):



wherein R_1 and R_2 are independently H, lower alkyl or lower acyl;

R_3, R_4, R_5, and R_6 are independently H or lower alkyl;

R_7, R_8 and R_9 are independently H, hydroxy, lower alkoxy or lower acyloxy; and

R_{10}, R_{11}, R_{12} and R_{13} are independently H or lower alkyl.

Lower alkyl is intended to generally mean C_1 -C_6, alkyl,and preferably R_3 and R_4 are C_1 –C_3 alkyl. Lower acyl is intended to generally mean C.sub.1 -C.sub.6 acyl, with C_2 -C_6 acyl being preferred. The formula is directed to both the phenolic compounds and the conventional esters and ethers thereof.

(Emphasis supplied) (Howell, Col 5, lines 10-41).

It is noted that neither section cited by the examiner is from the Detailed Description of The Invention and that the cited language of column 5 is not repeated in the Detailed Description.

To bring clarity to what Howell teaches, Applicants have engaged Dr. Raoul Tibes to review the present rejections, Howell and the present application. The Declaration of Raoul Tibes is filed herewith.

Properly placed in its context, Howell does not anticipate the present invention.

Howell does not teach the administration of NDGA and analogs thereof as sole agents to treat leukemia. Howell only teaches the administration of NDGA and analogs thereof together with antineoplastic drugs. Tibes at paragraph 12. Howell is singularly focused on the use of NDGA as an inhibitor of multidrug resistance ("MDR"). Tibes at paragraph 13.

The data presented by Howell does not support the use of NGDA as a single agent, that is, as an antineoplastic (anti-cancer) agent. Howell lacks data showing that NDGA is effective as a single agent to treat leukemia. Tibes at paragraph 14. Based on the data and assumptions presented by Howell, NGDA should not be given as single agent in to treat leukemia. Tibes at paragraph 15.

Howell nowhere in his application assumes single agent activity, nor defines or encompasses a molecular context that would lead a physician to use NDGA as a single agent to treat leukemia. See Howell, col 3 lines 65- col 4, lines 31. Tibes at paragraph 16. Howell properly cites studies showing that NDGA alone was ineffective in treating cancer. See Howell, column 4, lines 44-54.

> A clinical study was conducted by Smart, et al., reported in U.S. Pat. No. 4,880,637, in which human cancer patients ingested either a tea made from the creosote bush or doses of pure NDGA. This study indicated that neither NDGA nor the tea were effective anticancer agents and in some cases caused stimulation of tumor cell growth. This confirmed the earlier screening studies of NDGA conducted by Leiter, et al. of the Cancer Chemotherapy National Service Center of National Cancer Institute which obtained negative results when NDGA was tested against several types of cancer cells.

Tibes at paragraph 17.

Howell is concerned with treatment of MDR. MDR resistance mechanisms as far as they are known, define a specific molecular and cellular context, that is the presence of various MDR genes/proteins that exert/modify special biological/physiological functions leading to drug resistance to common (cytotoxic)-chemotherapies (or antineoplastic agents/drugs). Tibes at paragraph 18.

The field of MDR and clinical testing to overcome such resistance has been extensively studied over the last decades. Howell states that the "present invention contributes to solving the MDR problem". This again emphasizes that the invention teaches only to overcome MDR resistance. MDR resistance becomes of importance in association with agents used to treat cancer. An MDR modifying

agent could have single agent activity. This is however not assumed by Howell to be true for NGDA. Tibes at paragraph 19.

Addressing MDR mechanisms in cancer, combination therapy is required. That means a second agent, here the anti-neoplastic agent, needs to be present in order for the MDR concept to address what it is trying to overcome: resistance to an anti-neoplastic agent. Tibes at paragraph 20.

There are no known single agents used to overcome MDR mechanisms. If such an agent was present, it would have single agent activity and not follow the MDR concept as Howell claims to have overcome with his invention. This is also reflected in the fact that clinical studies trying to overcome MDR in cancer patients have often used combinations in those studies. This is in contrast to many other novel agents investigated which are studied in the clinic as single agents only, assuming to find at least some single agent activity. Tibes at paragraph 21.

An oncologist reading Howell would understand that Howell clearly rejects the activity of NDGA as single agent and assumes that NDGA does not have antineoplastic activity: "The NGDA compound and antineoplastic agent .." (column 4, lines 6-9). Further Howell states that "..one or more antineoplastic or cytotoxic agents with NGDA or an analog of NGDA..." (column 4, lines 11-13). Thus Howell itself clearly separates antineoplastic (anti-cancer) activity from the activity of NGDA and does not mention, assume or imply that NGDA does have single agent activity as an antineoplastic agent. Tibes at paragraph 22.

Howell's working examples 1-8 do not contain data suggesting that NDGA works as a single agent to treat leukemia. In examples 2-8 which contain data, the NDGA is administered with a separate antineoplastic agent. Tibes at paragraph 23.

Howell does not teach the use of the compounds tetra-O-methyl nordihydroguaiaretic acid or meso-1 ,4-bis[3,4-(dimethylaminoacetoxy)phenyl]-(2R,3S)dimethylbutane.

The present claims exclude the administration of NDGA. Howell contains no data on the efficacy of a single as such Howell cannot anticipate the present invention.

2. **The sequence of administration of NDGA with an antineoplastic agent does not support an inference that a single agent may be used.**

The examiner has taken the position that because Howell teaches that NDGA can be administered before, simultaneously with, or after an antineoplastic agent that Howell teaches administration of NDGA alone to treat the leukemia. As noted in the Tibes Declaration at paragraph 34, timing of administration is irrelevant when administering MDR inhibitors as long as it occurs during a treatment cycle. One of skill in the art would consider any administration during a treatment cycle co administration

3. **Howell is not enabled for the treatment of leukemia with NDGA as the only antineoplastic drug.**

Assuming, *arguendo*, that Howell is not limited to the use of NDGA in combination with an antineoplastic agent, and applying the factors set forth in *In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)*, it is clear that the Howell patent does not provide sufficient guidance for one of skill in the art to identify the claimed invention, namely the treatment of leukemia using only an NDGA derivative of a specified structure:

(1) a significant quantity of experimentation would be required to reach the present invention,

(2) no guidance is provided on how to use NDGA alone to treat leukemia . See Tibes paragraphs 12-16.

(3) there are no working examples showing the use of NDGA alone, Tibes at paragraph 23.

(4) the invention is a pharmaceutical intended for human use requiring utmost care,

(5) the prior art in fact teaches away from the use of NDGA alone to treat cancer,

Howell on its face teaches away from the use of NDGA alone:

> In accordance with the method of the present invention, an antineoplastic or cytotoxic agent is administered **in combination** (before, together and/or after) with NDGA (masoprocol) or an analog of NDGA in accordance with general Formula (I) set forth below, or a pharmaceutically

acceptable salt thereof, hereinafter collectively referred to as NDGA compounds.

The **NDGA compound and antineoplastic agent** can be co-administered simultaneously or sequentially with the NDGA compound preceding and/or following administration of the antineoplastic agent.

The invention also relates to a pharmaceutical or biologically active composition that comprises **one or more antineoplastic or cytotoxic agents with NDGA** or an analog of NDGA as set forth in said Formula, or a pharmaceutically acceptable salt thereof.

Masoprocol is a new MDR modulating agent. We have discovered that the combination of masoprocol known as nordihydroguaiaretic acid (hereinafter sometimes referred to as NDGA) or certain analogues thereof in combination with cytotoxic agents, e.g., Doxorubicin, Daunorubicin, Amsacrine, Mitoxantrone, Dactinomycin, Ellipticine, Etoposide, Teniposide, Chlorambucil, Melphalan, Cyclophosphamide, Nitrosoureas (BCNU, CCNU, MeCCNU), Methotrexate, Trimetrexate, 5-FU, Ara-C, Ara-A, Cisplatin, Carboplatin and Taxol can overcome multidrug resistance of certain diseased cells and has the potential of being effective in the treatment of solid malignant tumors, e.g., brain, breast, colon, lung, ovarian cancers and hematological malignant disorders including lymphoma, leukemia (acute nonlymphocytic leukemia, acute myelocytic leukemia), or increase the therapeutic effectiveness of the above-mentioned cytotoxic agents.

(Emphasis supplied) Howell, col 3 line 65- col 4, line 31.

(6) While the relative skill of those in the art is very high, (7) the art is unpredictable as shown by Howell in recounting the failures of NDGA treatment, and (8) the claims are limited to species of NDGA derivatives not taught by Howell.

As such Howell is not enabled for administration of NDGA derivatives other than NDGA as a single agent to treat leukemia.

For all of the above reasons, Applicant asserts that the presently claimed invention is not anticipated by Howell. Reconsideration and withdrawal of the 35 USC §102 rejection is respectfully requested.

b. **Obviousness**

The Examiner has maintained his rejection of claims 9, 10, 15, 18-20 and 32-33 under 35 USC §103 as being obvious in view of Howell. This rejection is traversed for the following reasons.

As noted above, Howell when placed in its proper context is only enabled for the use of NDGA as an MDR inhibitor to be administered with an antineoplastic agent. Tibes at paragraphs 12 and 42.

As such a *prima facie* case of obviousness has not been made. Further, the Howell reference does not disclose the NDGA derivatives which are specifically claimed by the present invention.

One of skill in the art upon reading Howell would not be motivated to use NDGA or its derivatives as a single agent to treat leukemia. Tibes at paragraph 43.

The obviousness analysis must include an assessment of (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed subject matter, (3) the level of ordinary skill in the art, and (4) any objective evidence of nonobviousness, often referred to as secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). The "secondary considerations" relating to the obviousness inquiry include commercial success, long felt need, copying, and the recognition of the patent by others. Id. An inquiry into such secondary considerations is an essential and integral part of the required analysis. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

Howell only teaches the administration of NDGA together with antineoplastic drugs. Tibes at paragraph 12. One of skill in the art would not expect that leukemia could be treated by the administration of an NDGA alone as described by Howell. Tibes at paragraph 43.

The present invention teaches that specific NDGA derivatives, administered by themselves, are effective against leukemia cells. This is not shown in the art.

The level of skill in the art is high but so is the unpredictability of the art as shown by the lack of efficacy seen in treating cancer with NDGA as shown by Howell.

In view of the above, the present claims are not obvious over Howell. Tibes at paragraph 40.

Applicant asserts that the present invention is not obvious in view of Howell because Howell fails to teach or suggest all of the elements of the claims. Applicants respectfully request all rejections based on 103 be withdrawn.

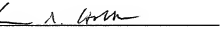
II. Double Patenting Rejections

Applicants will consider filing a Terminal Disclaimer if the rejection is maintained when otherwise allowable subject matter has been indicated.

CONCLUSION

Reconsideration and early allowance are respectfully requested. The Examiner is invited to contact the undersigned attorney in the event such conversation would facilitate moving this application forward.

Dated: December 1, 2009

By: 

Ann S. Hobbs, Ph.D.
Registration No. 36,830
Venable LLP
P.O. Box 34385
Washington, D.C. 20043-9998
Telephone: (202) 344-4000
Telefax: (202) 344-8300
ashobbs@venable.com